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Applicants	:	Jean F. Welter et al.
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For	:	APPARATUS AND METHOD FOR TISSUE ENGINEERING
Group Art Unit	:	1797
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Commissioner for Patents
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Alexandria, VA 22313-1450

APPEAL BRIEF

Sir:

Following the Notice of Appeal filed January 14, 2011, Appellants present this Appeal Brief.

I. REAL PARTY IN INTEREST

The real party in interest is Case Western Reserve University. An assignment of this application to Case Western Reserve University was recorded May 4, 2007, Reel/Frame: 019250/0385.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

III. STATUS OF CLAIMS

Claims 1-44 are currently pending in this application. Claims 15-41 have been withdrawn as being directed to unelected species. Claims 1-9, 12, 14, 43, and 44 stand rejected under 35 U.S.C. §102 as being anticipated by Vetillard (WO 0206441) - see English language equivalent (US 20040132175) for a translation. Claims 1-14 and 42-44 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Vetillard in view of Jensen (US20040077075). The rejections of claims 1-14 and 42-44 are appealed.

IV. STATUS OF AMENDMENTS

A Response After Final Rejection was filed December 14, 2010. No amendments to the claims have been made after the Final Office Action of July 14, 2010. An Advisory Action dated December 27, 2010 indicated that the Response After Final Rejection was considered but did not place the application in condition for allowance. The rejections of claims 1-14 and 42-44 were maintained.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 1 recites a bioreactor (10) that includes a housing (12) defining a first chamber (30) that contains a first liquid medium (31) (Page 7, lines 4-

5 and 23-27; Figs. 2-5). At least one gas permeable membrane (22 or 24) defines at least a portion of the housing (12) (Page 7, lines 13-19 and Page 10, lines 22-29; Figs. 2-5). The membrane (22 or 24) allows gas flow through the housing (12) into the first chamber (30) (Page 14, lines 10-13 and Figs. 2-5). A hydrostatic loading module (14) transmits hydrostatic pressure through the membrane (22 or 24) to the first liquid medium (31) contained in the first chamber (30) (Page 16, lines 14-21 and Figs. 2-5).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. Whether claims 1-9, 12, 14, 43, and 44 are anticipated by Vetillard.

B. Whether claims 1-14 and 42-44 are unpatentable over Vetillard in view of Jensen.

VII. ARGUMENTS

A. Applicable Law

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). 35 U.S.C. §103 forbids issuance of a patent when "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." In making a determination of obviousness under 35 U.S.C. §103(a):

> …the scope and contents of the prior art are determined; the differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill

> in the pertinent art resolved. Against this background, the obviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. Graham v. John Deere, 383 U.S. 1, 17-18, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966).

In *KSR Int'l. Co. V. Teleflex, Inc.*, the Supreme Court provided further direction on establishing a case of *prima facie* obviousness by noting that following the principles set forth in *Graham v. John Deere*:

> …may be more difficult … because the claimed subject matter may involve more than the simple substitution of one known element for another or the mere application of a known technique to a piece of prior art ready for the improvement. Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, *this analysis should be made explicit. Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741; 2007 U.S. Lexis 4745; 167 L. Ed. 2d 705; 75 U.S.L.W. 4289 (2007) (emphasis added).

Also, in *KSR Int'l. Co. V. Teleflex, Inc.*, the U.S. Supreme Court noted that the analysis supporting a rejection under 35 U.S.C. §103(a) should be made explicit, and that it was "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements in the manner claimed." *KSR* at 1741.

In considering the question of *prima facie* obviousness, the Federal Circuit has consistently held that when a rejection under 35 U.S.C. §103 is based upon a modification of a reference that destroys the intent, purpose, or function of the invention disclosed in the reference, such a proposed modification is not proper and the *prima facie* case of obviousness cannot be properly made. See, *In re Gordon,* 733 F.2d 900, 221 USPQ1125 (Fed. Cir. 1984). Also, it is improper to combine references where the references teach away from their combination. *In re Grasselli,* 713 F.2d 791, 743, 218 USPQ 769, 779 (Fed. Cir. 1983); See also, MPEP §2145 X.D.2. Further, if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). "[k]nown disadvantages in old devices which would naturally discourage search for new inventions may be taken into account in determining obviousness." *United States v. Adams,* 383 U.S. 39, 52, 148 USPQ 479, 484 (1966).

The legal concept of *prima facie* obviousness is a procedural tool of examination which applies broadly to all arts. It allocates who has the burden of going forward with production of evidence in each step of the examination process. See *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. If the examiner does not produce a *prima facie* case, the applicant is under no obligation to submit evidence of nonobviousness. See MPEP §2142.

B. Claims 1-9, 12, 14, 43, and 44

Claim 1

Claim 1 recites a bioreactor that includes a housing defining a first chamber that contains a first liquid medium. At least one gas permeable membrane defines at least a portion of the housing. The membrane allows gas flow through the housing into the first chamber. A hydrostatic loading module transmits hydrostatic pressure through the membrane to the first liquid medium contained in the first chamber.

The Examiner asserts that Vetillard expressly meets all the limitations of the claim except for the recitations directed to transmitting hydrostatic pressure. The Examiner alleges, however, that reciting a loading module that transmits hydrostatic pressure constitutes a recitation of intended use and, thus, the prior art need only *be capable of* performing the intended use to anticipate the claimed subject matter (Final Office Action page 9). The Examiner further asserts that structural limitations must be added to further define claim 1, or it must be persuasively argued that Vetillard is incapable of practicing the claimed intended use (Final Office Action page 9).

Claim 1 is not anticipated by Vetillard because: (1) the recitation in claim 1 that a hydrostatic loading module transmits hydrostatic pressure through a membrane is a functional limitation and not a recitation of intended use; (2) Vetillard does not teach or suggest the subject matter recited in claim 1; (3) the bioreactor of Vetillard is incapable of transmitting hydrostatic pressure; and (4) structural similarities between Vetillard and illustrated embodiments of the present invention are irrelevant in assessing whether Vetillard anticipates claim 1.

1. <u>The recitation in claim 1 that a hydrostatic loading module transmits hydrostatic pressure through a membrane is a functional limitation and not a recitation of intended use</u>

The MPEP states that claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure, *e.g.,* statements of intended use (MPEP §2111.04). In the present case, claim 1 positively recites a hydrostatic – not hydrodynamic – loading module. Moreover, claim 1 positively recites a hydrostatic loading module that not only is capable of transmitting hydrostatic pressure through a membrane, but a loading module *that actually transmits* hydrostatic pressure through the membrane. In other words, claim 1 does not make optional, but actually requires 1) a *hydrostatic* loading module that 2) *actually transmits* hydrostatic pressure through a membrane.

In fact, the recitation that the hydrostatic loading module transmits hydrostatic pressure is a functional recitation and not a statement of intended use. More specifically, claim 1 recites structure, *i.e.,* the hydrostatic loading module, which performs a specific function, *i.e.,* transmitting hydrostatic pressure through the membrane to the first liquid medium. Since the recitations in claim 1 are not optional but structural and functional these recitations are not directed to statements of intended use and, thus, they must be given patentable weight.

Courts have noted that there is nothing inherently wrong with defining some part of an invention in functional terms. <u>In re Swinehart</u>, 439 F.2d 210 (CCPA 1971). In particular, the <u>Swinehart</u> court noted that:

> "Functional" terminology may render a claim quite broad. By its own literal terms a claim employing such language

> covers any and all embodiments which perform the recited function. . . That is not to say, however, that every claim containing "functional" terminology is broad. Indeed, in many cases it will be obvious that only a very limited group of objects will fall within the intended category.

Id. at 213. Along those lines and according to the MPEP, a functional limitation must be evaluated and considered, just like any other limitation of the claim, for what it fairly conveys to a person of ordinary skill in the pertinent art in the context in which it is used. MPEP §2173.05(g) (emphasis added). The only instance in which functional language is not given patentable weight occurs when the functional limitations are found to be inherent in the prior art. In re Schreiber, 128 F.3d 1473 (Fed. Cir. 1997). This is not the case here.

In claim 1, one having ordinary skill would readily understand, in light of the specification, that which the Appellants are claiming by reciting that the hydrostatic loading module transmits hydrostatic pressure through the membrane to the first liquid medium (*see* Page 13, lines 25-28 and Page 16, line 14-27; Fig. 2 of the specification). These recitations are clear and definite to one having ordinary skill and, thus, are not overly broad. These limitations define the interrelations and functions of the hydrostatic loading module, the membrane, and the first liquid medium, and the specification clearly defines which features perform these functions and how those functions are performed. Accordingly, all limitations, including the functional limitations of claim 1, must be given patentable weight.

2. Vetillard does not teach or suggest the subject matter recited in claim 1

Vetillard does not teach or suggest 1) a hydrostatic loading module or 2) a hydrostatic loading module that actually transmits hydrostatic pressure through a

membrane. The Examiner asserts that zones C1 and C3 in Vetillard constitute hydrostatic loading modules and that the "downward phase" and "ascending phase" are created by varying pressure within the hydrostatic loading modules (Final Office Action page 2). In Vetillard, however, these phases are always conducted under hydrodynamic – not hydrostatic – conditions. In particular, Vetillard teaches that, during the downward phase, the pump P1 continually circulates nutritive media F1 from the vessel R1, through the zone C1, and back into the vessel (Figs. 2 and 6). In other words, the nutritive media F1 is not fluidly isolated or otherwise held static within the zone C1 at any time. Accordingly, the nutritive media F1 is constantly moving through the zone C1 and thereby applies hydrodynamic pressure p1 through the membrane M1 and into the zone C2. The pressure p1 forces waste products to drain from the zone C2, though the membrane M3, into the zone C3, and out of the system via a valve V3 (Fig. 2). This drainage is accomplished while the pump P3 is inactive, *i.e.*, when no fluid is supplied to the zone C3 and, thus, no pressures of any kind are exerted from the zone C3 towards the membrane M3 during the descending phase. Therefore, the only forces present during the downward phase are hydrodynamic forces.

Likewise, during the ascending phase, the pump P3 circulates dynamic liquid media F3 from the tank R3, through the zone C3, and into the waste disposal tank (Fig. 6). In other words, the liquid media F3 is not fluidly isolated or otherwise held static within the zone C3 at any time. Accordingly, the liquid media F3 is constantly moving and applies hydrodynamic pressure p3 through the membrane M3 and into the zone C2, thereby causing nutrients in the media F3 to ascend through the

zone C2 and into the zone C1 to replenish the tank R1 of fresh nutrient media F1 (Fig. 3). This replenishing is accomplished while the pump P1 is inactive, *i.e.*, when no fluid is supplied to the zone C1 and, thus, no pressures of any kind are exerted from the zone C1 towards the membrane M1. Therefore, the only forces present during the ascending phase are hydrodynamic forces.

In fact, Vetillard teaches that this inversion of flow from the zone C2 back into the zone C1 makes it possible to create trans-membrane flows subjected to low hydrodynamic stresses compatible with the fragility of the cultivated cells. Thus, a system of "laminar" slow flows is obtained (Paragraph 144 – emphasis added). Based on the foregoing, it is clear that any pressure applied through the membranes M1 or M3 is due to hydrodynamic forces. In other words, neither the zone C1 with liquid media F1 nor the zone C3 with liquid media F3 constitutes a hydrostatic loading module that transmits hydrostatic pressure through a membrane. Accordingly, Vetillard does not teach or suggest the subject matter recited in claim 1.

3. The bioreactor of Vetillard is incapable of transmitting hydrostatic pressure

The Examiner asserts that since the physical structure of the claimed invention and that of Vetillard are identical, there is no reason to believe that the Vetillard system is incapable of being operated according to the hydrostatic pressure intended use recited in claim 1 (Final Office Action pages 9-10). In particular, the Examiner asserts that the Vetillard bioreactor is fully capable of imparting a hydrostatic pressure on the culture chamber C2 by closing fluid outlet valves to seal the chambers C1, C3 surrounding the culture chamber (Final Office Action pages 9-10). The Appellants disagree.

As noted, the liquid media F1, F3 in Vetillard flow through the zones C1 and C3, respectively, to apply hydrodynamic pressure to the zone C2. As clearly shown in Fig. 6, however, neither of the zones C1, C3 is capable of being sealed with liquid media F1, F3 therein in order to hydrostatically load the zone C2. In particular, Fig. 6 shows that the pump P1 pumps liquid media F1 from the tank R1, through the zone C1, and back into the tank. There are no valves, however, on either the fluid intake or output side of the zone C1 that would allow the zone to be sealed with liquid media F1 therein. In fact, there are only two possible modes of operation for the zone C1, namely, 1) the zone C1 is filled with moving liquid media F1 in order to apply hydrodynamic pressure to the zone C2 or 2) the zone C1 is empty, *i.e.,* the pump P1 is shut off. Therefore, the bioreactor of Vetillard is incapable of applying hydrostatic pressure to the zone C2 via the zone C1.

Regarding the zone C3, Fig. 6 illustrates that the pump P3 pumps liquid media F3 from the tank R3, through the zone C3, and into the waste disposal tank. The conduit connected to the outlet tube of the zone C3 is equipped with a valve V3, possibly controlled by a regulation-control unit, which makes it possible to regulate and control the volume and the flow of the liquid media F3 circulating in open circuit in the zone C3 (Paragraph 117). Fig. 6, however, clearly illustrates that there is no valve on the intake side of the zone C3, *i.e.*, between the pump P3 and the zone C3. In other words, there is no way to statically isolate the liquid media F3 within the zone C3 regardless of whether the valve V3 is open or closed. Therefore, the bioreactor of Vetillard is incapable of applying hydrostatic pressure to the zone C1 via the zone C3.

For these reasons, it is clear that the bioreactor of Vetillard is incapable of fluidly isolating either of the liquid media F1 or F3 within the respective zone C1 or C3 in order to apply hydrostatic pressure to the zone C2. Accordingly, regardless of whether the Examiner considers the recitation of a hydrostatic loading module that transmits hydrostatic pressure to constitute a recitation of intended use or a functional limitation, the bioreactor of Vetillard is not capable of operating in this manner or performing this function.

4. Structural similarities between Vetillard and illustrated embodiments of the present invention are irrelevant in assessing whether Vetillard anticipates claim 1 and, nevertheless, there are substantial structural differences between the bioreactors in Vetillard and the present invention

It is well established that it is the function and purpose of claims, not the written description part of the specification itself, to delimit the right to exclude. Markman V. Westview Instruments, Inc., 52 F.3d 967, 980, 34 USPQ2d 1321, 1330 (Fed. Cir. 1995) (en banc). If structural claims were to be limited to devices operated precisely as a specification-described embodiment is operated, there would be no need for claims. Crystal Semiconductor Corp. v. TriTech Microelectronics International, Inc., 246 F.3d 1336, 1345-46, 1347, 57 USPQ2d 1953 (Fed. Cir. 2001). Moreover, courts have noted that limitations appearing in the specification will not be read into the claims, and that interpreting what is *meant* by a word *in* a claim 'is not to be confused with adding an extraneous limitation appearing in the specification, which is improper' Intervet America, Inc. v. Kee-Vet Laboratories, Inc., 887 F.2d 1050, 1053, 12 USPQ2d 1474, 1476 (Fed. Cir. 1989). Likewise, adding limitations to claims not required by the claim terms themselves, or unambiguously

required by the specification . . . is impermissible. Gary v. Logitech, Inc., 254 F.3d 1334, 1342-43, 59 USPQ2d 1290 (Fed. Cir. 2001).

In other words, any structural similarities between a prior art reference and an embodiment illustrated and described in an application are inconsequential in determining whether the prior art reference teaches the positively recited subject matter claimed in the application. In the present case, since claim 1 positively recites a 1) *hydrostatic* loading module 2) *that transmits* hydrostatic pressure any structural similarities between the cell culture chamber in Vetillard and a particular embodiment of the bioreactor system 10 illustrated in the drawings of the present invention are wholly irrelevant in assessing whether Vetillard teaches the subject matter positively recited in claim 1.

The Examiner asserts that since the bioreactor taught in Vetillard is almost identical to the Appellant's disclosed bioreactor, there is support for the conclusion that the Vetillard pumps, valves, and flow lines may be operated in order to produce hydrostatic pressure within the chambers C1, C3 (Final Office Action page 10) (emphasis added). As noted, however, neither of the chambers C1, C3 is capable of being fluidly isolated in order to apply hydrostatic pressure to the culture chamber C2. Since the structure of Vetillard does not support the teaching of a hydrostatic loading module, while the Appellant's disclosure supports such a module, not only is the Vetillard bioreactor not almost identical to the Appellant's disclosed bioreactor as the Examiner asserts but, in fact, there are necessarily substantial differences between the Appellant's disclosure and the teachings of Vetillard. Based on the foregoing, it is respectfully submitted that claim 1 is not anticipated by Vetillard and,

thus, it is respectfully submitted that claim 1 is patentable over Vetillard and is therefore allowable.

Claim 2

Claim 2 recites that the hydrostatic loading module transmits pressure by a static second liquid medium. As noted, Vetillard teaches a bioreactor in which both the fresh nutrient media F1 and the liquid media F3 are continually in motion while being perfused through the zones C1 and C3, respectively. Accordingly, Vetillard does not teach or suggest a hydrostatic loading module that transmits pressure by a static second liquid medium. For these reasons, it is respectfully submitted that claim 2 is patentable over Vetillard and is therefore allowable.

Claims 3-9, 12, and 14

Claims 3-9, 12, and 14 depend from claim 1 and are allowable for at least the same reasons as claim 1 and for the specific limitations recited therein.

Claim 43

Claim 43 recites that the inlet port and the outlet port are sealed during hydrostatic loading to allow the hydrostatic pressure of the first chamber to be increased without loss of first liquid medium from the first chamber. Vetillard does not teach or suggest this subject matter. As clearly shown in Fig. 6 of Vetillard, there is no indication that any of the modules C1, C2, C3 can be sealed during operation of the cell culture chamber in either the descending phase (Fig. 2) or the ascending phase (Fig. 3). Accordingly, Vetillard does teach or suggest the subject matter of claim 43 and, thus, it is respectfully submitted that claim 43 is patentable over Vetillard and is therefore allowable.

Claim 44

Claim 44 recites that the second chamber is sealed to pressurize the second liquid medium and thereby transmit hydrostatic pressure through the gas permeable membrane and into the first chamber. As noted, there is no indication that any of the modules C1, C2, C3 in Vetillard can be sealed during operation of the cell culture chamber in either the descending phase (Fig. 2) or the ascending phase (Fig. 3). Accordingly, Vetillard does teach or suggest the subject matter of claim 44 and, thus, it is respectfully submitted that claim 44 is patentable over Vetillard and is therefore allowable.

C. Claims 1-14 and 42-44

Claim 1

Claim 1 recites a bioreactor that includes a housing defining a first chamber that contains a first liquid medium. At least one gas permeable membrane defines at least a portion of the housing. The membrane allows gas flow through the housing into the first chamber. A hydrostatic loading module transmits hydrostatic pressure through the membrane to the first liquid medium contained in the first chamber.

It is respectfully submitted that a *prima facie* case of obviousness has not been shown because one having ordinary skill would not modify Vetillard to include the teachings of Jensen because modifying the bioreactor of Vetillard to operate under hydrostatic pressure as taught in Jensen changes the principle of operation of the Vetillard bioreactor. More specifically, (1) the inlet and outlet couples feeding the bioreactor of Vetillard are specifically positioned for hydrodynamic loading; (2) the inner walls of the bioreactor of Vetillard are specifically configured to promote a

homogenous distribution of the dynamic liquid media; (3) the inner walls of the bioreactor of Vetillard are configured to minimize stress upon the membranes during hydrodynamic loading; and (4) the regulation control unit of Vetillard is specifically constructed and configured to continually adjust and modify the characteristics and volume of moving fluids. Regardless, Jensen does not cure the deficiencies of Vetillard because one having ordinary skill, seeking to modify the bi-directional, alternating dynamic fluid media bioreactor of Vetillard, would not look to the single direction, single fluid media bioreactor of Jensen.

Vetillard teaches that dynamic fluid media F1 is selectively circulated through the zone C1 in order to supply growth hormones and large proteins to the culture chamber C2 while draining wastes from the culture chamber. Likewise, the dynamic fluid media F3 is selectively circulated through the zone C3 in order to replenish the fluid media F1 with fresh nutritive elements from the fluid media F3 (Paragraphs 138 and 141; Figs. 2-6).

The Examiner asserts that if Vetillard does not disclose transmitting hydrostatic pressure into the culture chamber C2 and if limitations in claim 1 drawn to the transmission of hydrostatic pressure do not represent an intended use, then Vetillard fails to anticipate claim 1 (Final Office Action page 5). The Examiner further asserts, however, that Jensen teaches the transmission of hydrostatic pressure in the culturing of cells via microfermentation (relying on paragraphs 67-74, 190, and 194). The Examiner concludes that it would have been obvious to one having ordinary skill to modify Vetillard such that hydrostatic pressure is capable of promoting diffusion of desired compounds through the membranes M1, M2, and that

only minor (if any) structural alterations would be necessary to generate hydrostatic pressure within the apparatus of Vetillard (Final Office Action pages 6 and 11). The Appellants disagree.

As noted, neither of the chambers C1, C3 in Vetillard is capable of being fluidly isolated in order to transmit hydrostatic pressure to the culture chamber C2. Furthermore, the bioreactor in Vetillard is specifically configured and designed to promote the circulation of the dynamic fluid media F1 and F3 through the bioreactor in order to culture cells within the culture chamber C2 via hydrodynamic pressure. Accordingly, modifying Vetillard to cease the flow of the dynamic fluid media F1 and F3 in order to achieve hydrostatic pressure changes the principle of operation of the Vetillard bioreactor and, thus, such a modification would not be obvious to one having ordinary skill.

1. <u>The inlet and outlet couples feeding the bioreactor of Vetillard are specifically positioned for hydrodynamic loading</u>

Vetillard teaches that the bioreactor is intended to be fed with three distinct dynamic liquid media F1-F3 via three characteristic inlet and outlet couples. As clearly shown in Fig. 1, each pair of inlet and outlet couples is longitudinally and angularly offset from one another relative to the central axis of the bioreactor. In particular, the three inlet and outlet couples EF1-EF3 and SF1-SF3, respectively, of the dynamic liquid media F1-F3 are positioned in three vertical planes passing through the axis of symmetry of the bioreactor. These planes are shifted by an angle of about 60^0 between the first inlet couple and the second inlet couple and by an angle of about 120^0 between the first inlet couple and the third inlet couple (Paragraphs 100 and 103). The shifted location of these inlet and outlet couples

delimiting the culture chamber make it possible to obtain a homogeneity of distribution of the liquid media within the chamber during hydrodynamic flow through the culture chamber (Paragraph 97). In other words, each pair of inlet and outlet couple is specifically positioned to allow dynamic fluid media to proficiently cultivate the cells within the culture chamber C2 via hydrodynamic pressure.

If, however, the bioreactor was intended to operate under hydrostatic pressures such a configuration of the inlet and outlet couples would be unnecessary. In other words, the flow path of the fluid media F1 and F3 across either side of the culture chamber C2 affects the transfer of nutrients and waste through the membranes M1, M2 to such an extent that the inlet and outlet couples are strategically and purposefully positioned offset from one another.

2. <u>The inner walls of the bioreactor of Vetillard are specifically configured to promote a homogenous distribution of the dynamic liquid media</u>

The internal sides of the two end walls of the bioreactor, *i.e.*, the inward-facing sides of the top and bottom walls of the bioreactor shown in Fig. 1, are smooth so that the distribution of the dynamic liquid media F1, F3 feeding the culture chamber C2 and in contact with the feeding and dialysis membranes M1, M3 can be realized in a homogenous manner (Paragraph 71). Moreover, the inner sides of the two end walls are equipped with a network of main and secondary grooves that ensure a homogenous distribution of the liquid media F1, F3 with a good dispersion of the dynamic liquid media in the culture chamber C2 (Paragraphs 72-73). The secondary grooves are also sized and oriented to facilitate the drainage and evacuation of the dynamic liquid media F1, F3 from the chambers C1, C3 (Paragraph 74).

If, however, the bioreactor of Vetillard was intended to operate under hydrostatic pressures such a configuration of the inner walls of the bioreactor would be unnecessary. In other words, the homogenous distribution of the dynamic fluid media F1, F3 through the chambers C1, C3 is so vital to operation of the bioreactor that the inner walls of the bioreactor were provided with a complex network of distribution grooves. Vetillard clearly made every effort to ensure the efficacy of a hydrodynamically loaded bioreactor.

It is clear from the above that if the bioreactor were configured or intended to be operated under hydrostatic pressures, Vetillard would not have made concerted efforts to position the inlet and outlet couples or configure the inner walls of the bioreactor in the specific manner described. More specifically, if the bioreactor in Vetillard was intended to use hydrostatic pressure, the distribution of fluid media F1, F3 across either side of the culture chamber C2 would always be homogeneous because the media would be held static within the respective zone C1, C3 as opposed to flowing through the zones along a fixed path as is the case in the current hydrodynamic operation of the bioreactor. Therefore, Vetillard would not purposefully position the inlet and outlet couples or configure the inner walls of the bioreactor in the precise manners shown and described if a homogenous distribution of media could be established via hydrostatic pressurization. Accordingly, the precise inlet and outlet positioning and configuration of the inner walls of the bioreactor are evidence that Vetillard did not contemplate the use of hydrostatic pressure.

3. <u>The inner walls of the bioreactor of Vetillard are configured to minimize stress upon the membranes during hydrodynamic loading</u>

Vetillard also teaches that by providing the bioreactor with smooth inner walls the dynamic liquid media F1, F3 may flow over the membranes M1, M3 without stress. In other words, Vetillard specifically configures the bioreactor to reduce the amount of stress upon the membranes. If, however, the bioreactor were operated hydrostatically as the Examiner asserts, the stress on the membranes M1, M3 would rise significantly. Since Vetillard clearly seeks to minimize the stress on the membranes M1, M3, significantly increasing the stress on the membranes by operating the bioreactor under hydrostatic conditions is undesirable and undermines the objectives of Vetillard.

4. <u>The regulation control unit of Vetillard is specifically constructed and configured to continually adjust and modify the characteristics and volume of moving fluids</u>

Additionally, a regulation control unit in the bioreactor is used to receive information related to the dynamic fluid media F1-F3 and alters the various tanks, pumps, valves, and pressures existing in the zones C1-C3 of the culture chamber in order to modify, on request, the internal characteristics of the culture chamber and to change the parameters and the programs of regulation contributing to the homeostasy of the media in order to adjust to the cultivated cellular type (Paragraphs 110-111). Collectively, the devices of the bioreactor make it possible to maintain the homeostasy of the culture chamber by pre-conditioning the flows of the dynamic fluid media F1-F3 which penetrate into it in order not to enter the culture chamber an element of volume of culture media which could induce brutal disturbance of its physicochemical parameters (Paragraph 120).

In other words, as with the precisely oriented inlet and outlet couples and the presence of the complex network of distribution grooves in the inner walls of the bioreactor, the regulation control unit of Vetillard is specifically constructed and configured to continually adjust and modify the characteristics and volume of *moving* fluids, *e.g.,* the dynamic fluid media F1, F3 entering the zones C1, C3, in order to maintain homeostasy in the culture chamber. If the bioreactor was intended to hydrostatically apply pressure to the culture chamber, the entire regulation control unit would have to be redesigned. Based on the foregoing, it is clear that the bioreactor of Vetillard is not intended to be operated under hydrostatic pressures, and modifying the bioreactor of Vetillard to operate hydrostatically would frustrate the objectives of Vetillard and be in opposition to every concerted effort taken by Vetillard to operate the bioreactor hydrodynamically.

5. <u>One having ordinary skill, seeking to modify the bi-directional, alternating dynamic fluid media bioreactor of Vetillard, would not look to the single direction, single fluid media bioreactor of Jensen</u>

The teachings of Jensen do not negate the fact that it is undesirable to modify the bioreactor of Vetillard to operate hydrostatically. Moreover, the bioreactor in Jensen supplies a culture medium with oxygenated water or medium on a single side of the culture medium in a single direction (Fig. 2A). On the other hand, the bioreactor of Vetillard supplies cells in a culture chamber C2 with dynamic liquid media F1 rich in growth factors, *i.e.*, rich nutrient media, on one side of the culture chamber in one direction and a dynamic liquid media F3 completely deprived of growth factors, *i.e.*, basic-regenerating nutritive media, on the other side of the culture chamber in an opposite direction in an alternating, dynamic fashion. In other

words, while the bioreactors of Jensen and Vetillard are both directed to culturing cells, the bioreactors operate in completely different manners and perform completely different functions. Therefore, one having ordinary skill, seeking to modify the bi-directional, alternating dynamic fluid media bioreactor of Vetillard, would not look to the single direction, single fluid media bioreactor of Jensen. Accordingly, one having ordinary skill would not modify Vetillard to operate under hydrostatic pressures as taught in Jensen. For these reasons, a *prima facie* case of obviousness has not been shown and, thus, it is respectfully submitted that claim 1 is patentable over the combination of Vetillard and Jensen and is therefore allowable.

Claim 2

Claim 2 recites that the hydrostatic loading module transmits the pressure by a static second liquid medium. As noted, Vetillard does not teach or suggest using static fluids to cultivate cells within the culture chamber C2. Jensen does not cure the deficiencies of Vetillard because the teachings of Jensen do not negate the fact that is undesirable to modify Vetillard to operate under hydrostatic pressure and the bioreactors of Vetillard and Jensen operate in completely manners. Accordingly, it is respectfully submitted that claim 2 is patentable over the combination of Vetillard and Jensen and is therefore allowable.

Claims 3-14

Claims 3-14 depend from claim 1 and are allowable for at least the same reasons as claim 1 and for the specific limitations recited therein.

Claim 42

Claim 42 recites that two membranes having substantially identical gas permeability are positioned on opposite sides of the first chamber. It is respectfully submitted that a *prima facie* case of obviousness has not been shown because modifying Vetillard to have identical membranes as taught in Jensen would destroy the intent and purpose of the Vetillard device.

Vetillard explicitly teaches that an object of the invention is to maintain a good cellular viability within the culture chamber and bioreactor by providing, on the one hand, to the cells of the culture media a nutrient supply in an adequate amount and, on the other hand, by evacuating the waste and the inhibitor elements generated in order to allow a growth of the cell population. Another object of the invention is to be able to recycle the growth factors of the media while sufficiently evacuating cell wastes from the culture media to thereby achieve economic optimization of the cells culture (Paragraphs 12-13). Accordingly, the membranes M1 and M3 in Vetillard are specifically configured to have different constructions, namely, different cutting thresholds of .2-.4µm and 10-12KDa, respectively (Paragraphs 41-42) in order to accomplish the dual objective of draining waste in one direction and replenishing the nutrient media tank in the other.

The Examiner asserts that one having ordinary skill in the art would have recognized that it would be beneficial to ensure that the Vetillard membranes were identical if both of the membranes interact with the same type of culture fluid or are intended to perform the same function (Final Office Action page 8). Based, however, on the explicit teachings of Vetillard the dynamic liquid media F1 and F2 must be

different in order for the bioreactor to properly function and the membranes M1 and M3 are never intended to perform the same function. As noted, Vetillard teaches that the bioreactor is designed to achieve economic optimization of the cells culture by recycling the growth factors of the media while sufficiently evacuating the cell wastes from the culture media. In other words, Vetillard states that multiple functions are performed on the cell culture by surrounding the cell culture with two different liquid media F1 and F2 and allowing the respective functions, *i.e.,* growth factor recycling and waste removal, to be performed through two membranes M1 and M3 having different cutting thresholds. In fact, Vetillard differentiates the membranes by designating each with the specified function each performs, namely, the feeding membrane M1 and the dialysis membrane M3 (Paragraphs 41-42).

More specifically, the first liquid media F1 is specifically designed to feed the culture media in nutrient elements rich in growth factors (Paragraph 86). On the other hand, the second liquid media F2 is specifically designed to 1) introduce the cells to be cultivated into the chamber; 2) transport vectors of gene transfer and allow their setting in contact with the cells to establish a membrane fusion between the target cells and the vector of gene transfer; and 3) rinse the flow of inhibiting macromolecules present within the chamber (Paragraphs 88-89 and 92). Due to the different functions performed by the first and second liquid media F1 and F2, the membranes separating the liquid media from the cell culture must necessarily have different gas permeability, otherwise the operability and effectiveness of the bioreactor would be significantly frustrated.

If for example, the first and second membranes M1 and M3 both had a cutting threshold of .22 µm, the growth hormones and large proteins provided by the first media F1 would be allowed to pass through the second membrane and into the waste disposal tank (*see* Figs. 4-6), thereby rendering the bioreactor incapable of replenishing the vessel R1 of fresh nutrient media during the ascending phase (Fig. 3). Therefore, the particularized functionality of the first and second liquid media F1 and F2 requires two different liquid media and therefore two membranes having different gas permeability. This is further evidenced by Vetillard repeatedly emphasizing the use of several *distinct* liquid media (*e.g.,* Paragraphs 85 and 96) as well as the used of membranes having *different* cutting thresholds (*e.g.,* Paragraphs 42 and 48). Accordingly, Vetillard does not teach, suggest or even contemplate using two substantially identical culture fluids or culture fluids that are intended to perform the same function as the Examiner asserts. For these reasons, one having ordinary skill would not modify Vetillard to exhibit identical or similar culture fluids or membranes having substantially the same gas permeability as such a modification would clearly destroy the intent and purpose of the bioreactor of Vetillard.

The teachings of Jensen do not negate the undesirable effects of modifying Vetillard to utilize identical media F1 and F2 or to exhibit multiple membranes having substantially identical gas permeability. Accordingly, Jensen does not cure the deficiencies of the multi-function bioreactor taught by Vetillard. Based on the foregoing, modifying the bioreactor of Vetillard as proposed would destroy the intent and purpose of the bioreactor of Vetillard and, thus, the proposed modification of

Vetillard would not be obvious to one having ordinary skill. For these reasons, a *prima facie* case of obviousness has not been shown and, thus, it is respectfully submitted that claim 42 is patentable over the combination of Vetillard and Jensen and is therefore allowable.

Claim 43

Claim 43 recites that the inlet port and the outlet port are sealed during hydrostatic loading to allow the hydrostatic pressure of the first chamber to be increased without loss of first liquid medium from the first chamber. Vetillard does not teach or suggest this subject matter. As clearly shown in Fig. 6 of Vetillard, there is no indication that any of the modules C1, C2, C3 can be sealed during operation of the cell culture chamber in either the descending phase (Fig. 2) or the ascending phase (Fig. 3).

Furthermore, as noted, the bioreactor in Vetillard is specifically tailored to 1) operate under hydrodynamic pressure and 2) minimize stress on the membranes M1, M3. Therefore, one having ordinary skill in the art would not modify Vetillard to operate hydrostatically or in a manner that increases the stress, *i.e.*, pressure, on either of the membranes M1 and M3 and, thus, one having ordinary skill would not modify Vetillard to exhibit the structure recited in claim 43. Jensen does not cure the deficiencies of Vetillard. In particular, Jensen does not change the fact that it is undesirable to modify the bioreactor of Vetillard to operate hydrostatically or in a manner that increases the stress on the membranes M1, M3. For these reasons, a *prima facie* case of obviousness has not been shown and, thus,

it is respectfully submitted that claim 43 is patentable over the combination of Vetillard and Jensen and is therefore allowable.

Claim 44

Claim 44 recites that the second chamber is sealed to pressurize the second liquid medium and thereby transmit hydrostatic pressure through the gas permeable membrane and into the first chamber. As noted, there is no indication that any of the modules C1, C2, C3 in Vetillard can be sealed during operation of the cell culture chamber in either the descending phase (Fig. 2) or the ascending phase (Fig. 3).

Furthermore, as noted, the bioreactor in Vetillard is specifically tailored to 1) operate under hydrodynamic pressure and 2) minimize stress on the membranes M1, M3. Therefore, one having ordinary skill in the art would not modify Vetillard to operate hydrostatically or in a manner that increases the stress, *i.e.*, pressure, on either of the membranes M1 and M3 and, thus, one having ordinary skill would not modify Vetillard to exhibit the structure recited in claim 44. Jensen does not cure the deficiencies of Vetillard. In particular, Jensen does not change the fact that it is undesirable to modify the bioreactor of Vetillard to operate hydrostatically or in a manner that increases the stress on the membranes M1, M3. For these reasons, a *prima facie* case of obviousness has not been shown and, thus, it is respectfully submitted that claim 44 is patentable over the combination of Vetillard and Jensen and is therefore allowable.

VIII. APPENDICES

Appendix A attached contains a copy of the claims on appeal.

IX. EVIDENCE APPENDIX

The attached Evidence Appendix contains no evidence.

X. RELATED PROCEEDINGS APPENDIX

The attached Related Proceedings Appendix contains no related proceedings.

Please charge any deficiency or credit any overpayment in the fees for this Appeal Brief to our Deposit Account No. 20-0090.

Respectfully submitted,

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APPENDIX A

Claim 1 (Previously Presented): A bioreactor comprising:

a housing defining a first chamber that contains a first liquid medium, the housing including an inlet port and an outlet port for fluid flow of the liquid medium through the first chamber, the liquid medium including at least one of a growth or culture medium for growing or culturing cells in the first chamber;

at least one gas permeable membrane defining at least a portion of the housing, the membrane allowing gas flow through the housing into the first chamber; and

a hydrostatic loading module that transmits hydrostatic pressure through the membrane to the first liquid medium contained in the first chamber.

Claim 2 (Original): The bioreactor of claim 1, the hydrostatic loading module transmitting the pressure by a static second liquid medium.

Claim 3 (Original): The bioreactor of claim 1, the hydrostatic loading module being attached to the housing and forming a second chamber with the housing, the second chamber containing a second liquid medium and being separated from the first chamber by the gas permeable membrane.

Claim 4 (Original): The bioreactor of claim 3, the hydrostatic loading module including at least one pump for increasing or decreasing the pressure of the second liquid medium in the second chamber.

Claim 5 (Original): The bioreactor of claim 3, the hydrostatic loading module being capable of increasing or decreasing the hydrostatic pressure in the first chamber.

Claim 6 (Original): The bioreactor of claim 4, the hydrostatic loading module further including a pressure sensor for monitoring the pressure in the second chamber.

Claim 7 (Original): The bioreactor of claim 1, the housing including a frame, the frame including a first surface, a second surface spaced apart and aligned with the first surface, and an opening that extends through the frame from the first surface to the second surface.

Claim 8 (Original): The bioreactor of claim 7, the housing including a first gas permeable membrane attached to the first surface of the frame and a second gas permeable membrane attached to the second surface of the frame, the first gas permeable membrane, the second gas permeable membrane, and the frame defining the first chamber.

Claim 9 (Original): The bioreactor of claim 1, the hydrostatic loading module being attached to the housing and including a second chamber and a third chamber, the second chamber and the third chamber containing a second liquid medium and

being separated from the first chamber by, respectively, a first gas permeable membrane and a second gas permeable membrane.

Claim 10 (Original): The bioreactor of claim 1, the at least one gas permeable membrane having sufficient optical transparency to permit visual observation of the first chamber.

Claim 11 (Previously Presented): The bioreactor of claim 10, the at least one gas permeable membrane being resistant to cell attachment.

Claim 12 (Original): The bioreactor of claim 1, further including a pH sensor, the pH sensor measuring the pH of the first liquid medium entering the first chamber and exiting the first chamber.

Claim 13 (Original): The bioreactor of claim 1, further including an impeller for circulating the first liquid medium in the first chamber.

Claim 14 (Previously Presented): The bioreactor of claim 1, including a first flow control valve positioned in the inlet port and a second flow control valve positioned in the outlet port, the first flow control valve and the second flow control valve regulating the flow of the first liquid medium through the first chamber.

Claim 15 (Withdrawn): A bioreactor comprising:

a housing defining a first chamber, a second chamber, and a first gas permeable membrane separating the first chamber and the second chamber and allowing gas flow between the first chamber and the second chamber, the first chamber containing a first liquid medium and including an inlet port and an outlet port for fluid flow of the first liquid medium through the chamber, the first liquid medium being used to culture or grow cells or tissue in the first chamber, the second chamber containing a second liquid medium and including an inlet and outlet for fluid flow of the second liquid medium through the second chamber; the hydrostatic pressure of the second liquid medium being transmitted through the first gas permeable membrane to affect the hydrostatic pressure of the first liquid medium contained in the first chamber.

Claim 16 (Withdrawn): The bioreactor of claim 15, further including at least one pump for increasing or decreasing the pressure of the second liquid medium in the second chamber.

Claim 17 (Withdrawn): The bioreactor of claim 16, further including a pressure sensor for monitoring the pressure in the second chamber.

Claim 18 (Withdrawn): The bioreactor of claim 15, the housing including a frame, the frame including a first surface, a second surface spaced apart and aligned

with the first surface, and an opening that extends through the frame from the first surface to the second surface.

Claim 19 (Withdrawn): The bioreactor of claim 18, the gas permeable membrane being attached to the first surface of the frame, and the housing further including a second gas permeable membrane attached to the second surface of the frame, the first gas permeable membrane, the second gas permeable membrane, and frame defining the first chamber.

Claim 20 (Withdrawn): The bioreactor of claim 19, including a third chamber, the third chamber containing the second liquid medium and being separated from the first chamber by the second gas permeable membrane.

Claim 21 (Withdrawn): The bioreactor of claim 20, the first gas permeable membrane and the second gas permeable membrane having sufficient optical transparency to permit visual observation of the first chamber.

Claim 22 (Withdrawn): The bioreactor of claim 15, the first gas permeable membrane being resistant cell attachment.

Claim 23 (Withdrawn): The bioreactor of claim 15, further including a pH sensor, the pH sensor measuring the pH of the first liquid medium entering the first chamber and exiting the first chamber.

Claim 24 (Withdrawn): The bioreactor of claim 15, further including an impeller for circulating the first liquid medium in the first chamber.

Claim 25 (Withdrawn): The bioreactor of claim 1, the inlet port including a first flow control valve and the outlet port including a second flow control valve, the first flow control valve and the second flow control valve regulating the flow of the first liquid medium through the first chamber.

Claim 26 (Withdrawn): A bioreactor comprising:

a housing defining a first chamber that contains a first liquid medium and a plurality of cells, the housing including an inlet port and an outlet port for fluid flow of the liquid medium through the first chamber, the liquid medium including at least one of a growth or culture medium for growing or culturing the plurality of cells in the first chamber;

at least one gas permeable membrane defining at least a portion of the housing, the membrane allowing gas flow through the housing into the first chamber; and

a hydrostatic loading module for transmitting hydrostatic pressure through the membrane to the first liquid medium and the plurality of cells contained in the first chamber.

Claim 27 (Withdrawn): The bioreactor of claim 26, the plurality of cells contained in the first chamber being seeded on at least one of a scaffold or sponge.

Claim 28 (Withdrawn): The bioreactor of claim 27, the plurality of cells comprising mesenchymal stem cells.

Claim 29(Withdrawn): The bioreactor of claim 28, the mesenchymal stem cells being treated with a cytokine to promote differentiation into chondrogenic tissue.

Claim 30 (Withdrawn): The bioreactor of claim 28, the mesenchymal stem cells being aggregated prior to being seeded on the scaffold or sponge.

Claim 31 (Withdrawn): The bioreactor of claim 30, the hydrostatic loading module being attached to the housing and forming a second chamber with the housing, the second chamber containing a second liquid medium and being separated from the first chamber by the gas permeable membrane.

Claim 32 (Withdrawn): The bioreactor of claim 26, the hydrostatic loading module being attached to the housing and including a second chamber and a third chamber, the second chamber and the third chamber containing a second liquid medium and being separated from the first chamber by, respectively, a first gas permeable membrane and a second gas permeable membrane.

Claim 33(Withdrawn): The bioreactor of claim 26, the plurality of cells being suspended in the first liquid medium.

Claim 34 (Withdrawn): The bioreactor of claim 26, the first liquid medium promoting chondrogenesis.

Claim 35 (Withdrawn): A method of preparing chondrogenic tissue construct, the method comprising:

isolating a plurality of mesenenchymal stem cells from bone marrow;

expanding the mesenchymal stem cells in a culture medium;

seeding the expanded mesenchymal stem cells onto a construct;

growing the seeded construct in a chondrogenic medium; and

hydrostatically loading the seeded construct while the seeded construct is grown in the chondrogenic medium.

Claim 36 (Withdrawn): The method of claim 35, the seeded construct being grown in the chamber of a bioreactor, the chamber being perfused with the chondrogenic medium, the bioreactor allowing for hydrostatic loading of the seeded construct in the bioreactor chamber, without removing the seeded construct from the chamber.

Claim 37 (Withdrawn): The method of claim 35, the hydrostatic loading being applied cyclically to the seeded construct.

Claim 38 (Withdrawn): The method of claim 35, the mesenchymal stem cells being treated with a cytokine to promote differentiation to chondrocytes.

Claim 39 (Withdrawn): The method of claim 38, the cytokine comprising fibroblast growth factor 2 (rhFGF-2).

Claim 40 (Withdrawn): The method of claim 35, further comprising,

providing a suspension of mesenchymal stem cells in a culture medium contained in a sterile vessel;

aggregating the mesenchymal stem cells in the vessel,

maintaining the aggregated mesenchymal stem cells in culture for a duration of time sufficient to allow chondrogenesis to begin;

releasing the mesenchymal stem cells from aggregate; and

seeding the construct with the released cells.

Claim 41 (Withdrawn): The method of claim 35, chondrogenic medium containing a first concentration of dexamethasone; and

reducing the concentration of dexamethasone in the chondrogenic medium during growing to a second concentration substantially less than the first concentration, the second concentration of the dexamethasone being effective to induce the expression of BMP-2 in the cells.

Claim 42 (Previously Presented): The bioreactor of claim 1, the at least one gas permeable membrane comprising two membranes having substantially identical gas permeability and being positioned on opposite sides of the first chamber.

Claim 43 (Previously Presented): The bioreactor of claim 1, the inlet port and the outlet port being sealed during hydrostatic loading to allow the hydrostatic pressure of the first chamber to be increased without loss of first liquid medium from the first chamber.

Claim 44 (Previously Presented): The bioreactor of claim 3, the second chamber being sealed to pressurize the second liquid medium and thereby transmit hydrostatic pressure through the gas permeable membrane and into the first chamber.

EVIDENCE APPENDIX

None.

RELATED PROCEEDINGS APPENDIX

None.